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Spanish Stem Cell Bank Interviews Examine the Interest of Couples in Donating Surplus Human IVF Embryos for Stem Cell Research

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Human embryonic stem cells (hES cells) were first derived in 1998 and hold great promise for opening up new avenues in regenerative medicine through the generation of transplantable cells to be used in future cell replacement therapies (Menendez et al., 2006; Reubinoff et al., 2000; Thomson et al., 1998). However, there is extensive discussion about ethical aspects of the use of human embryos for stem cell research (Edwards, 2005; ESHRE Taskforce on Ethics and Law, 2001, 2002; McLaren, 2001). Part of this discussion relates to intense public debate about the ethics and implications of in vitro fertilization (IVF) and its associated procedures (Edwards and Beard, 1997). In IVF treatment cycles, the number of embryos generated usually exceeds the number that can be prudently transferred to the future mother, and these surplus embryos can potentially be used for stem cell research. The 2003 SART-RAND study estimated that at that time there were 400,000 stored embryos in 430 US IVF clinics (Hoffman et al., 2003; Kaiser Network, 2007). In Spain, the estimate is that in 2003 there were 100,000 stored embryos in 203 Spanish IVF clinics. In other countries, the specific legislative environment influences both the numbers of stored embryos and their potential availability for donation for stem cell research (see, for example, Koeferl Puorger et al. [2006]).

Despite being a very Catholic country, Spain currently represents a fairly permissive legal and ethical environment for the use of excess embryos for hES cell research. Although IVF cycles must not be planned specifically for the generation of human embryos to be used for stem cell research, cryopreserved embryos fewer than 14 days past fertilization may be used for hES cell line derivation regardless of the length of time that they have been kept frozen. Moreover, the Spanish government recently passed a bill to permit therapeutic cloning and cellular reprogramming. The only requirement for hES cell line derivation and use is that the procedures must be linked to a specific research project. Many countries, including Spain and the UK, have set up stem cell banks to provide researchers with hES cell lines and facilitiate hES cell research. Although UK and Swedish legislation allow the use of fresh embryos, most countries only permit donation of spare cryopreserved embryos for biomedical research. Importantly, while embryos are becoming more accessible for physicians and embryologists who work within IVF units, access to embryos for basic researchers in stem cell centers and academic institutions not directly linked to an IVF clinic remains a major challenge.

Stem cell banks such as ours need to derive new hES cell lines for both international distribution and for our own hES cell research projects. To investigate the interest of Spanish couples in donating supernumerary cryopreserved embryos for hES cell research, we have conducted interviews with 97 couples covering two IVF units. We conducted an extensive analysis through personal interviews in which couples were asked to make a decision about the fate of embryos cryopreserved for more than 3 years in public IVF units not linked to the stem cell bank. The interviews were carried out by a senior embryologist and a legal advisor and were supervised by the head of the IVF clinic. The law in many countries does not allow embryo donation for the treatment of other infertile couples (Bjuresten and Hovatta, 2003). Spanish law, however, like U.S. legislation, does permit this alternative (Hoffman et al., 2003). Thus, current Spanish law obliged us to offer the couples four options regarding the fate of the surplus cryopreserved embryos: (1) to keep the embryos cryopreserved for potential future reproductive purposes, (2) to donate embryos to other infertile couples for reproductive purposes, (3) to donate the embryos to biomedical research (including stem cell research), or (4) to discard the embryos. The four possible embryo fates were explained in detail to all the couples by the senior embryologist in an unbiased manner (Cortes et al., 2006). The interview included a brief summary of the couple's IVF cycle, covering the oocyte acquisition date, the number of embryos obtained, the number of embryos frozen, and the number of births. The legal situation and potential concerns of the couples about donation for biomedical research were addressed by the legal advisor and the senior embryologist. When the first option (to keep embryos cryopreserved for potential future reproductive purposes) was explained to the couples, it was made clear that the embryos could be frozen until the end of the fertility age of the woman, which would be assessed by a gynecologist. For the second option

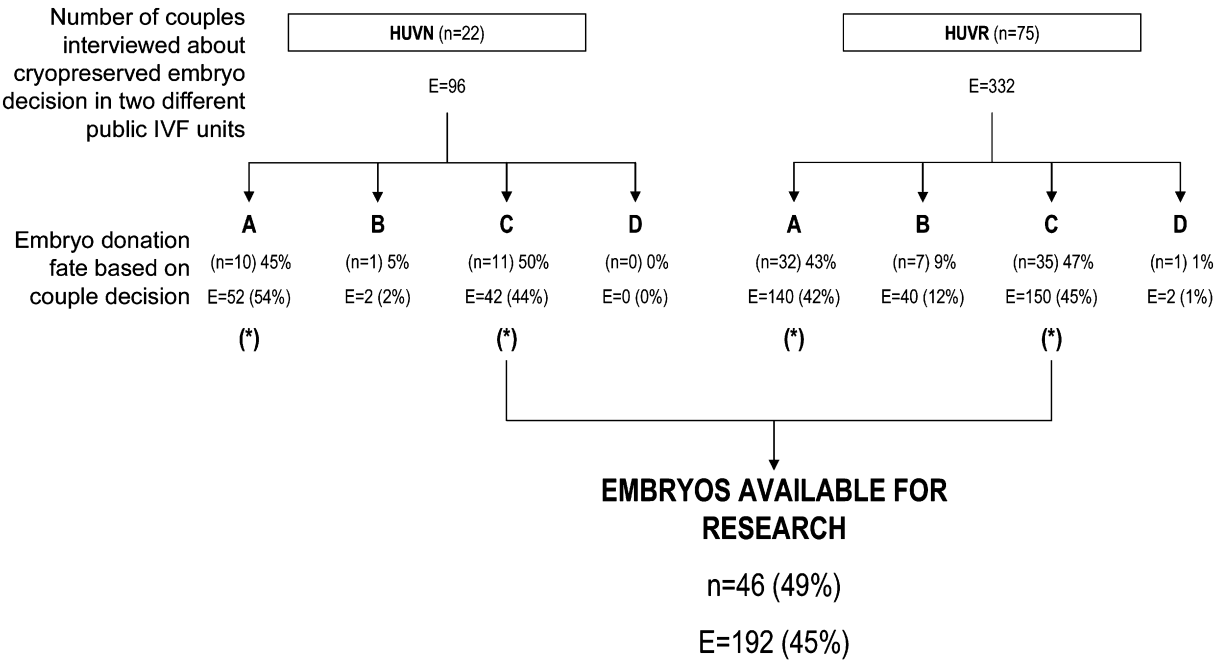

Figure 1. Summary of the Choices Made by Interviewed Couples about the Fate of Supernumerary Cryopreserved Human Embryos

Couples from two different Public IVF Public Units (HUVR and HUVN) were interviewed about the potential fate of their spare embryos that had been frozen for more than 3 years. In accordance with Spanish legislation, the couples were offered four options: (A) to keep the embryos cryopreserved for potential future reproductive purposes, (B) to donate embryos to other infertile couples for reproductive purposes, (C) to donate embryos to biomedical research (including stem cell research), or (D) to discard surplus embryos. The four possible embryo fates were explained in detail to all the couples by the senior embryologist and a legal advisor in an unbiased manner. HUVN, Virgen de las Nieves Hospital, Granada, Spain; HUVR, Virgen del Rocio Hospital, Seville, Spain; n, number of couples with embryos cryopreserved for more than 4 years. (E) Number of cryopreserved human embryos. *P value, (A) versus (B), $p < 0.00001$; (B) versus (C), $p < 0.00001$.

(donation of embryos to other infertile couples), it was made clear that this donation would be for reproductive ends and require renunciation of any resulting pregnancy. With respect to the third option (donation of embryos to research), the couples received up-to-date information about research projects being carried out in the field of stem cell research, including the derivation of hES cell lines and their possible future application in regenerative medicine and cell therapy, developmental biology, drug screening, disease modeling, and other areas. One stem cell research project was also explained in detail to accommodate the Spanish legal requirement that the donation of embryos must be related to a specific research project. Following the interview, couples were then asked to read, understand, and sign an informed consent form that, according to the Spanish law, was anonymous, confidential, voluntary, altruistic, and revocable. The legal advisor was present at all times to ensure that the interview was unbiased and allowed the couples to go through the decision-making process independently.

We found that 49% of the interviewed couples chose to donate their embryos for stem cell research, and 44% decided to keep them cryopreserved. Only 7% chose to donate them to other infertile couples, and less than 1% made the decision to discard them (Figure 1). Importantly, similar results were obtained from couples who underwent IVF cycles in IVF units in two cities with different social and economic profiles (Figure 1). These results differ from a recent report from a clinic in the U.S., which indicated that 54% of treated couples asked to have their embryos destroyed, 43% decided to donate them to biomedical research unrelated to stem cells (although donation for stem cell research was not discussed), and 3% offered them to other infertile couples (Kaiser Network, 2007). Furthermore, the more extensive SART-RAND study carried out in the U.S. in 2003 (Hoffman et al., 2003) found that only 2.8% of cryopreserved embryos were designated for stem cell research, which obviously limits possible conversion into hES cell lines (Hoffman et al., 2003).

It is worth emphasizing that, in our study, half of the interviewed couples opted to donate their surplus stored embryos for stem cell research. Although it should be stressed that the aims and execution of the two studies were clearly very different, our findings do contrast sharply with those described in the SART-RAND study published in 2003. In our view, there are a number of potential reasons for the differences, and we have outlined our perspective on the most significant of these in a summary table (Table 1). We consider the differences are likely due to the following. (1) the SART-RAND study's major aim being to determine, using a questionnaire, the number of embryos stored in IVF clinics and the number of embryos targeted for stem cell research. By contrast, we already knew in advance the

Table 1. Potential Reasons for the Differences in the Outcome of Embryo Donation for Stem Cell Research between Our Study and the Previously Published SART-RAND Study

Possible Reasons for the Differences between Studies	Hoffman et al. (2003)	Present Study
Percent of embryos donated to stem cell research	2.8%	45%
Aims of the study	(1) To determine the number of embryos stored in US IVF clinics	(1) To determine the percentage of couples willing to donate their embryos for stem cell research based on a cohort of patients with embryos frozen for more than 3 years and knowing in advance the pregnancy success rate
	(2) To determine prospectively the percentage of couples willing to donate their embryos for stem cell research	
Type of communication between the IVF clinic and queried couples	Questionnaire sent to the couples	Personal interview
Strategy to reduce confusion about ethical and research issues	Not evaluated	Presence during the interview process of a senior embryologist and head of the IVF clinic
Time of contact with the couples	Before or shortly after the IVF cycles	3–4 years after embryo cryopreservation with known pregnancy success rates approaching 40%

number of embryos frozen for more than 3 years and the pregnancy success rate, facilitating the interview process. (2) The SART-RAND study was conducted by sending a questionnaire to clinics but did not involve an interview. We instead undertook a time-consuming process in which we conducted formal interviews with all the couples as described above. We found that the interview process allowed us to address the couples' concerns about ethical and scientific questions. The interviews were conducted in an unbiased manner, but this level of personal attention could be a persuasive factor in terms of donation to research. (3) The SART-RAND survey included couples at many different stages of the IVF process, including before or just after the cycle, so it is likely that, in this scenario, most couples of reproductive age would choose to keep their embryos cryopreserved for potential future use. In our study, however, 97 couples with embryos frozen for more than 3 years were interviewed. At this stage, slightly more than 35% of couples had babies, and in fact nearly 30% of them had twins, while only a few had triplets. Clearly, such circumstances make the decision to donate surplus embryos for research more appealing. In fact, we suspect that if a similar survey using an interview process were carried out at this time with U.S. couples who have embryos preserved for 3 years or more, the outcome would be closer to our results than the earlier SART-RAND findings. The likelihood of such an outcome would be even greater if hES cell derivation was supported by U.S. government funding. Furthermore, although donation of fresh embryos is prohibited in many countries, a study carried out in a Sweden, where this process is permitted, found that a very high proportion (92%) of queried couples chose to donate embryos that were not of sufficient quality for implantation or cryopreservation for research purposes, including stem cell research, rather than to have them destroyed (Bjuresten and Hovatta, 2003). Thus, if the legislative conditions change, it is possible that discarded fresh embryos could also be a significant source of material for research.

To conclude, we have found that a personal interview with a senior embryologist and a legal advisor is productive in ascertaining the willingness of couples to donate embryos for stem cell research. The interview process helps couples navigate the confusing legal situation and can be used to alleviate any concerns they have about donation for research purposes. We hope that our findings will promote new initiatives among other stem cell researchers and experts in ethics and stem cell counseling to facilitiate progress in hES cell research.

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REFERENCES

Bjuresten, K., and Hovatta, O. (2003). Hum. Reprod. *18*, 1353–1355.

Cortes, J.L., Cobo, F., Barnie, A.H., Catalina, P., Cabrera, C., Nieto, A., Montes, R., and Concha, A. (2006). Cytotechnology *52*, 1–11.

Edwards, R.G. (2005). Reprod. Biomed. Online *10*, 1–8.

Edwards, R.G., and Beard, H.K. (1997). Hum. Reprod. *12*, 3–5.

ESHRE Taskforce on Ethics and Law (2001). Hum. Reprod. *16*, 1446–1448.

ESHRE Taskforce on Ethics and Law (2002). Hum. Reprod. *17*, 1409–1410.

Hoffman, D.I., Zellman, G.L., Fair, C., Mayer, J.F., Zeitz, J.G., Gibbons, W.E., and Turner, T.G. (2003). Fertil. Steril. *79*, 1063–1069.

Kaiser Network (2007). http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=42571.

Koeferl Puorger, U.P., Buergin, M., Wunder, D., Crazzolara, S., and Birkhaeuser, M.H. (2006). Reprod. Biomed. Online *13*, 772–777.

McLaren, A. (2001). Nature *414*, 129–131.

Menendez, P., Bueno, C., and Wang, L. (2006). Cytotherapy *8*, 530–541.

Reubinoff, B.E., Pera, M.F., Fong, C.Y., Trounson, A., and Bongso, A. (2000). Nat. Biotechnol. *18*, 399–404.

Thomson, J.A., Itskovitz-Eldor, J., Shapiro, S.S., Waknitz, M.A., Swiergiel, J.J., Marshall, V.S., and Jones, J.M. (1998). Science *282*, 1145–1147.